BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Patisiran (Onpattro™)

File Name:	patisiran_onpattro
Origination:	11/2018
Last CAP Review:	5/2020
Next CAP Review:	5/2021
Last Review:	5/2020

Description of Procedure or Service

Patisiran (Onpattro™) is a double-stranded small interfering ribonucleic acid (siRNA) that is indicated for the treatment of adults with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR).

Hereditary transthyretin-mediated amyloidosis (hATTR), formerly referred to as familial amyloid polyneuropathy (FAP), is a progressive, life-threatening disease caused by genetic mutations in the gene that encodes transthyretin (TTR). The mutant amyloid precursor protein (TTR) is produced by the liver, and in hATTR both mutant and wild-type TTR deposit as amyloid in multiple organ systems including the peripheral nerves, heart, kidneys, and gastrointestinal tract. The clinical presentation of hATTR is heterogeneous, and may cause neuropathic alterations leading to severe motor and sensory disruption and decline in ambulation and activities of daily living. Additional effects on the autonomic nervous system typically result in complications such as hypotension, urinary problems, impotence, and diarrhea. Cardiac manifestations of hATTR include fatal conduction abnormalities, arrhythmias, and heart failure. Given the progressive nature of the disease, average life expectancy of patients with hATTR is typically 7 to 12 years following diagnosis. Prior to the approval of patisiran (Onpattro), the available treatment options for hATTR have been limited and primarily included orthotopic liver transplantation (OLT) and transthyretin tetramer stabilizers, such as diflunisal or tafamidis. However, patients receiving these therapies often experience continued disease progression.

Patisiran (Onpattro), a transthyretin-directed small interfering RNA, was approved by the U.S. Food and Drug Administration (FDA) in August 2018, for the treatment of peripheral neuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients. It works by causing degradation of mutant and wild-type transthyretin (TTR) mRNA through RNA interference, resulting in reduced serum TTR protein and TTR protein deposits in tissues.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for patisiran (Onpattro™) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit

design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Patisiran (Onpattro) is covered

Initial Therapy

Patisiran (Onpattro) is considered medically necessary for the treatment of adult patients (≥18 years old) with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) when the following criteria are met:

1. The patient has a diagnosis of hATTR based on:
    a. Presence of clinical signs and symptoms, **and**
    b. Genetic testing confirms a pathogenic variant in *TTR*; **AND**
2. The patient has peripheral neuropathy associated with hATTR with:
    a. A baseline polyneuropathy disability score of IIIb or lower **OR** a baseline Familial Amyloid Polyneuropathy (FAP) stage of 1 or 2 (see Policy Guidelines), **and**
    b. Abnormal electrodiagnostic (nerve conduction) studies consistent with hATTR-associated polyneuropathy, **and**
    c. Other causes of peripheral neuropathy have been excluded; **AND**
3. The patient has not had prior liver transplantation; **AND**
4. Patisiran is prescribed by a neurologist or a specialist in the treatment of amyloidosis.

Initial authorization: 12 months

Continuation Therapy

Continuation of treatment with patisiran (Onpattro) beyond 12 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) when the following criteria are met:

1. The patient has received patisiran treatment previously, **and**
2. The patient continues to have a polyneuropathy disability score of IIIb or lower or FAP stage 1 or 2 (see Policy Guidelines), **and**
3. The patient has documentation of positive clinical response (e.g. improved neurologic impairment, motor function, quality of life, ambulation), **and**
4. Patisiran is prescribed by a neurologist or a specialist in the treatment of amyloidosis.

When Patisiran (Onpattro) is not covered

Patisiran (Onpattro) is considered **investigational** and therefore not covered when the above criteria are not met.

Policy Guidelines

Dosing and Administration

Onpattro is given as an intravenous (IV) infusion and should only be administered by a healthcare professional.

Onpattro dosing is based on actual body weight. For patients weighing less than 100kg, the recommended dosing regimen for Onpattro is 0.3 mg/kg once every 3 weeks. For patients weighing 100kg or more, the recommended dosing regimen is 30 mg once every 3 weeks. The dose is to be infused over approximately 80 minutes, and premedication with a corticosteroid, acetaminophen, and antihistamine should be given prior to each infusion.

According to the manufacturer's safety information for Onpattro, the most common adverse reactions (incidence ≥10%) include infusion-related reactions and upper respiratory tract infections. The patient should be monitored for signs and symptoms of infusion-related reactions during each infusion. Onpattro treatment leads to decreased serum vitamin A levels; thus, patients should receive vitamin A supplementation at the recommended daily allowance while receiving Onpattro therapy.

Clinical Trial Evidence

The efficacy and safety of patisiran was evaluated by the APOLLO study. This phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial assessed 225 adult patients with polyneuropathy caused by hereditary transthyretin amyloidosis. Patients included in the trial were required to have a diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy and a documented pathogenic variant in transthyretin (TTR). Eligible patients also had a Neuropathy Impairment Score (NIS) of 5 to 130 (range, 0-244), polyneuropathy disability (PND) score of ≤IIIb, and adequate liver function. Patients were randomized in a 2:1 ratio to receive either patisiran 0.3 mg/kg (n=148) or placebo (n=77) intravenously once every 3 weeks for 18 months. The primary endpoint was the change from baseline to 18 months in the modified Neuropathy Impairment Score+7 (mNIS+7), a composite neuropathy measure evaluating motor, sensory, and autonomic neuropathy (range, 0-304), which was significantly lower with patisiran than with placebo. The mean (±SD) mNIS+7 at baseline was 80.9±41.5 in the patisiran group and 74.6±37.0 in the placebo group, with a least-squares mean (±SE) change from baseline of -6.0±1.7 versus 28.0±2.6 (difference, -34.0 points; $p<0.001$) at 18 months. Other secondary endpoints included quality of life (scored by Norfolk Quality of Life-Diabetic Neuropathy [Norfolk QOL-DN] questionnaire, range -4 to 136), motor strength (measured by NIS-weakness score), disability (scored on the Rasch-built Overall Disability Scale), gait speed (measured by 10-m walk test), nutritional status (assessed by modified BMI scores), and patient-reported autonomic symptoms (measured by the Composite Autonomic Symptom Score-31 questionnaire). The change from baseline to 18 months in the Norfolk QOL-DN score was significantly lower in the patisiran group versus the placebo group. The mean (±SD) baseline Norfolk QOL-DN score was 59.6±28.2 for patisiran and 55.5±24.3 for placebo with a least-squares mean (±SE) change from baseline to 18 months of -6.7±1.8 versus 14.4±2.7 (difference, -21.1 points; $p<0.001$). Statistically significant differences favoring patisiran were demonstrated across all other secondary endpoints. Reduction in transthyretin serum levels were rapid and sustained in the patisiran group over 18 months with a median reduction of 81% (range, -38 to 95). Mild or moderate infusion-related reactions were observed in roughly 20% of patients receiving patisiran and 10% of those receiving placebo.

Assessment Tools

The polyneuropathy disability score is an additional assessment tool with ranking based on different classes I-IV. Higher scores are indicative of more impaired walking ability. The varying classes are defined as follows:

I: preserved walking, sensory disturbances
II: impaired walking without need for a stick or crutches
IIIa: walking with one stick or crutch
IIIb: walking with two sticks or crutches

IV: confined to wheelchair or bedridden

Familial Amyloid Polyneuropathy (FAP) clinical staging:

Stage 0: no symptoms
Stage 1: unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs
Stage 2: assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk
Stage 3: wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J0222*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Alnylam Pharmaceuticals, Inc. Onpattro (patisiran) lipid complex injection, for intravenous use. Highlights of prescribing information. August 2018. Available at: http://www.alnylam.com/wp-content/uploads/2018/08/ONPATTRO-Prescribing-Information.pdf. Accessed October 2018.

U.S. Food and Drug Administration. FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm616518.htm. Accessed October 2018.

Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):11-21.

Adams D, Suhr OB, Dyck PJ, et al. Trial design and rationale for APOLLO, a phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017;17(1):181.

Medical Director review 11/2018

Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3584981/pdf/1750-1172-8-31.pdf. Accessed January 2019.

Medical Director review 1/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.30, 2/14/2019

Specialty Matched Consultant Advisory Panel – 5/2019

Medical Director review 11/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.30, 2/13/2020

Specialty Matched Consultant Advisory Panel – 5/2020

Policy Implementation/Update Information

11/30/18 New policy developed. Onpattro is considered medically necessary for the treatment of adult patients (≥18 years old) with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR). Added HCPCS codes C9399 and J3490 to "Billing/Coding" section. References added. Medical Director review 11/2018. (krc)

12/31/18 Added HCPCS code C9036 to Billing/Coding section effective 1/1/19. (krc)

2/12/19 Added the following to "When Covered" section: "Family history and clinical signs and symptoms" for diagnosis confirmation, and "OR a baseline FAP stage of 1 or 2, and abnormal electrodiagnostic (nerve conduction) studies consistent with hATTR-associated polyneuropathy, and other causes of peripheral neuropathy have been excluded." Added the following to both initial and continuation sections of policy statement: "Patisiran is prescribed by a neurologist or a specialist in the treatment of amyloidosis." Within Policy Guidelines section, removed description of Neuropathy Impairment Score (NIS) and added FAP staging description. References added. Medical Director review 1/2019. (krc)

5/28/19 Reference added. Specialty Matched Consultant Advisory Panel review 5/15/2019. No change to policy intent. (krc)

10/1/19 Added HCPCS code J0222 to Billing/Coding section and deleted codes C9399, C9036, J3490 effective 10/1/19. (krc)

11/12/19 Under "When Covered" section, removed family history requirement for diagnosis of hATTR. Medical Director review 11/2019. (krc)

6/23/20 Reference added. Specialty Matched Consultant Advisory Panel review 5/20/2020. (krc)